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A resveratrol-loaded scaffold enhances tendon healing: Histological and biomechanical analysis in a rat Achilles tendon repair model

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MAIN POINTS

- This experimental study evaluates the effects of a novel bioabsorbable scaffold (Dermalix®), composed of collagen, laminin, and resveratrol-loaded microparticles, on tendon healing in a rat Achilles tendon model.
- Histological analysis demonstrated reduced fibroblast proliferation in the Dermalix® group compared to controls.
- Biomechanical testing showed significantly higher maximum load and stiffness values in the Dermalix® group at both 3 and 6 weeks post-operatively.
- Dermalix® appears to reduce peritendinous adhesions and may offer a promising adjunct for tendon repair surgeries by promoting organized healing.

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ABSTRACT

Aim: This study aims to evaluate the effects of Dermalix® (Dx), a resveratrol-loaded, bioabsorbable scaffold composed of collagen, laminin, and hyaluronic acid, on tendon healing and peritendinous adhesion formation following primary Achilles tendon repair in a rat model.

Materials and Methods: A total of 28 female Wistar Albino rats underwent bilateral Achilles tendon injury and repair using the modified Kessler technique. The right legs were treated with local Dx application over the repair site, while the left legs served as untreated controls. Animals were randomly assigned to one of four groups (n = 7 per group). The groups were defined by the evaluation time point (3 or 6 weeks) and the type of analysis (histological or biomechanical). Assessments included macroscopic adhesion scoring, histological quantification (counts of fibroblasts, fibrocytes, and vessels), and biomechanical testing (maximum load to failure and elongation at rupture). Statistical comparisons were made using t-test, Mann-Whitney U, chi-square, ANOVA, or the Friedman test, as appropriate for the data.

Results: Dx application significantly reduced severity of adhesion at both 3 and 6 weeks ($p<0.01$). Histological analyses revealed significantly lower fibroblast and fibrocyte counts with more organised collagen alignment in Dx-treated groups ($p<0.05$). Biomechanically, rupture force was significantly higher in Dx groups at both time points ($p<0.01$ and $p=0.029$), while no significant difference was found in elongation distance. The scaffold was resorbed by week 3, without inducing any foreign body reaction or systemic side effects.

Conclusion: The local application of Dx enhanced tendon healing significantly and reduced peritendinous adhesions without compromising biomechanical strength. Its bioabsorbable composition and local antioxidant properties make Dx a promising supportive local treatment option in tendon repair surgery. This is particularly valid in cases with high adhesion risk.

Keywords: Resveratrol, Bioabsorbable scaffold, Tendon healing, Peritendinous adhesion, Achilles tendon, Dermalix®

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INTRODUCTION

Tendon injuries are frequently encountered in clinical practice and may result in prolonged functional limitations, even following technically successful repairs [1]. Multiple therapeutic approaches have been investigated to enhance tendon regeneration. These approaches include biological agents such as cytokines, growth factors, and stem cells, as well as physical treatments like hyperbaric oxygen therapy. In addition, various biomaterials have been studied, including platelet concentrates, hyaluronic acid (HA), stem cell-derived microvesicles, and zinc oxide nanoparticles [2–4]. Although many adjuvant therapies have shown promise in both preclin-

ical and clinical studies, none have improved tendon healing consistently enough to justify routine adoption, highlighting the urgent need for new research to reduce the risk of long-term impairments [5,6].

Phytoalexins, found in many vegetables, especially grapevines, are protective substances synthesised by plants against ultraviolet radiation, bacterial and fungal infections [7]. Resveratrol (RSV) is a phytoalexin and has many benefits that stems from its potent antioxidant properties. Dermalix® (Abdi İbrahim İlaç San. ve Tic. A.S., Turkey) (Dx) is a patented bioabsorbable scaffold composed of collagen, laminin, and RSV-loaded microparticles. Initially developed for treatment of diabetic wounds. Its supportive role in the treatment of chronic wounds, regenerative potential and antioxidant properties suggest Dx may also enhance tendon repair [8–10].

This study aimed to investigate the effects of Dx, used as an adjuvant therapy, on the quality of tendon healing, healing rate, and peritendinous adhesion formation following primary tendon repair.

MATERIALS AND METHODS

Study design

This prospective, controlled, experimental animal study was approved by the Local Ethics Committee for Animal Experiments (Approval Date-No: 21.03.2023, 2023-05/08). All procedures were conducted in compliance with the Helsinki Declaration and international guidelines for the care and use of laboratory animals, including the ARRIVE guidelines. Measures were taken to minimise animal suffering, pain, and distress throughout the study. Housing, feeding, and care of the experimental animals were conducted by the principles outlined in the "Guide for the Care and Use of Laboratory Animals". Appropriate anaesthesia and analgesia protocols were applied to reduce postoperative pain and ensure animal welfare.

The sample size was determined based on previous studies evaluating biomechanical outcomes in tendon healing models [11]. To detect a 25% difference in mean rupture force between groups, with a standard deviation of 20%, an α-error of 0.05, and 80% power, the minimum required sample size was calculated as 7 tendons per group (effect size: 1.45). The analysis was performed using G*Power version 3.1.9.7 (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany).

Surgical model and experimental groups

Twenty-eight female Wistar Albino rats (250–300 g; 3–4 months old) were acquired from Bursa Uludağ University's Experimental Animal Research Unit (BUÜ - DENHAB). A convenience sampling method was used.

In each rat, a bilateral surgical procedure was performed on the Achilles tendons. Under anesthesia, a midline skin incision was made to expose the Achilles and plantaris tendons. The Achilles tendon was transected 0.3–0.5 cm proximal to its calcaneal insertion. To create a critical-size defect that impairs spontaneous recovery, a 3 mm segment of the tendon was excised. The plantaris tendon was left intact to serve as an internal splint. The severed Achilles tendon was then repaired using a modified Kessler technique with 5/0 non-absorbable suture.

A paired-limb design was used for treatment comparison. In each animal, the right leg was designated the treatment group, where Dx was applied to the repair line before skin closure (Figure 1). The left leg served as the control group and received no adjuvant therapy.

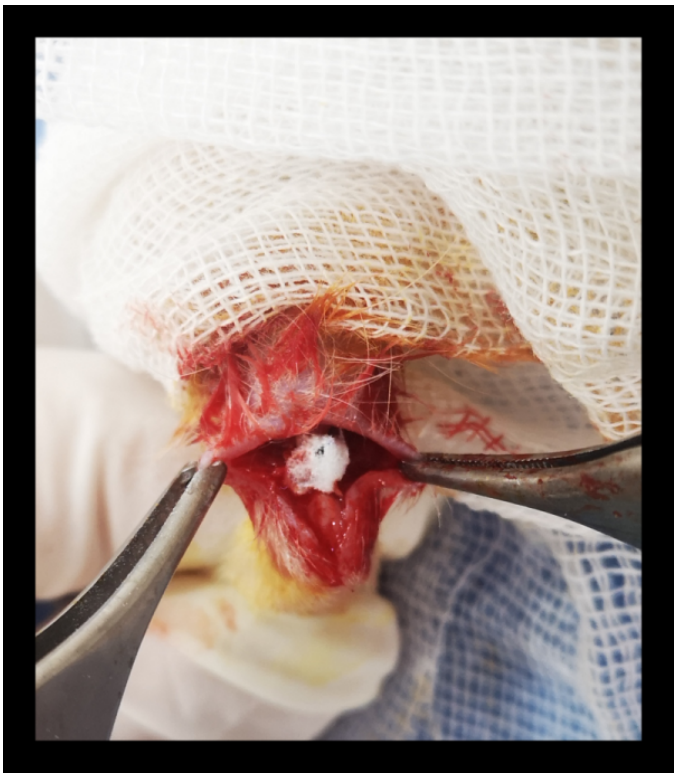

Figure 1. Intraoperative Photograph Demonstrating Dermalix® Application Over the Surgically Exposed Rat Achilles Tendon. Intraoperative view of the rat hind limb showing the exposed and surgically transected Achilles tendon following repair. Dermalix® scaffold has been applied over the repair site to facilitate healing and minimize peritendinous adhesions.

Following surgery, animals were housed at 20–22°C and 50–55% humidity with ad libitum access to food and water. The 28 rats were randomly allocated into four cohorts (n=7 per cohort) based on the planned endpoint analysis:

- Histology Week 3 (Hist3): Sacrificed at 3 weeks for histological evaluation.
- Biomechanics Week 3 (Bmc3): Sacrificed at 3 weeks for biomechanical testing.
- Histology Week 6 (Hist6): Sacrificed at 6 weeks for histological evaluation.
- Biomechanics Week 6 (Bmc6): Sacrificed at 6 weeks for biomechanical testing.

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Outcome assessments

To minimize observer bias, all histological and biomechanical assessments were performed by investigators blinded to the group allocations.

- Macroscopic Adhesion Scoring: Adhesion formation was graded using a semiquantitative scale: grade 1 (none), grade 2 (filmy), grade 3 (mild), grade 4 (moderate, 35–60% of area), and grade 5 (severe, >60% of area) [12].

- Histological Analysis: Tendon samples were fixed in 10% formaldehyde, embedded in paraffin, and sectioned at 5 μm. Sections were stained with haematoxylin and eosin (H&E) to assess tissue morphology and Masson's trichrome (MT) to evaluate collagen organization. Quantitative analysis included counts of fibroblasts, fibrocytes, and blood vessels oriented parallel to collagen fibers.

- Biomechanical Testing: Tendons were mounted in a tensile testing machine. After measuring the tendon diameter with a digital caliper, a tensile load was applied at a constant displacement rate of 10 mm/min until failure. The maximum rupture force and stiffness were recorded (Figure 2).

Primary endpoints

The primary endpoints were the histological quality of tendon healing (collagen fiber alignment, cellular density) and biomechanical tensile strength (maximum rupture force).

Statistical analysis

Statistical analysis was performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables as frequencies and percentages. Normality was assessed with the Shapiro-Wilk test. Between-group comparisons (Control vs. Dermalix) were made using the independent samples t-test or Mann-Whitney U test, depending on data distribution. The Chi-square test or Fisher's exact test was used for categorical variables. Intragroup comparisons over time were analyzed using repeated measures ANOVA or the Friedman test, with Bonferroni correction applied for post-hoc analyses. Spearman's correlation analysis was used to assess relationships between histological and biomechanical variables. $P < 0.05$ was considered statistically significant. P values were reported with two digits, or three digits if starting with zeros (e.g., $P = 0.002$). Values close to .05 were expressed to three decimals (e.g., $P = 0.053$); values < 0.001 were reported as $P < 0.001$.

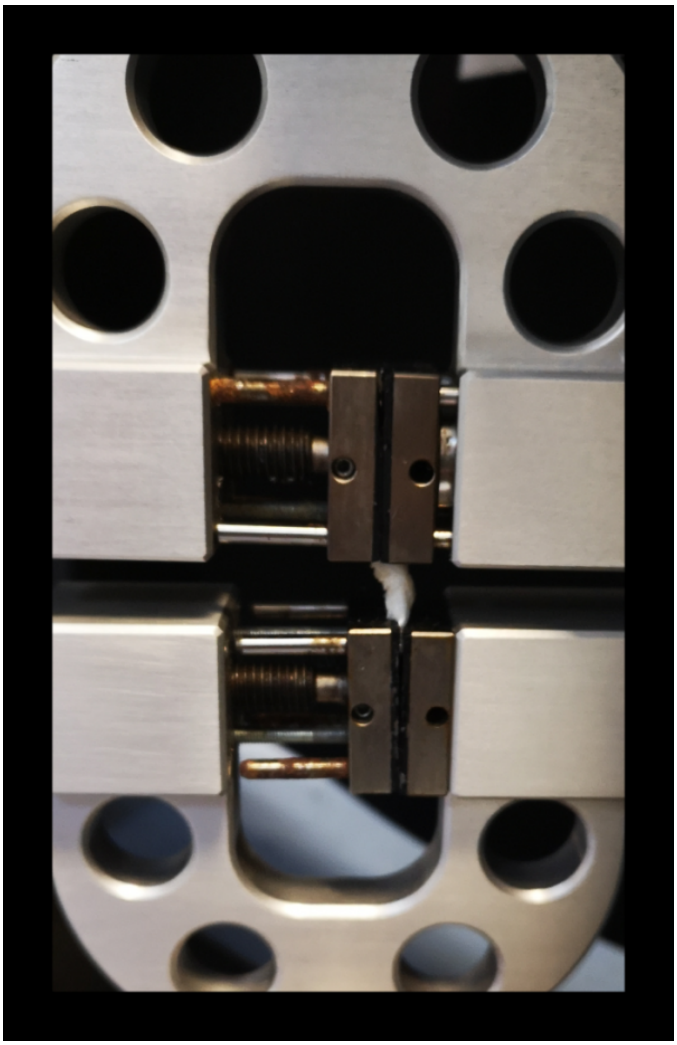

Figure 2. Mounting of the Achilles Tendon Specimen for Biomechanical Testing. Achilles tendon sample clamped between the opposing jaws of the tensile testing machine prior to biomechanical load-to-failure testing.

RESULTS

Macroscopic findings

Macroscopic evaluation revealed that the treatment significantly reduced adhesion formation. At both the 3- and 6-week time points, the control groups (CG) exhibited moderate to severe adhesions, with no instances of mild or no adhesions. In contrast, the majority of rats in the treatment groups (DxG) developed either no or only mild adhesions. This difference between the control and treatment groups was statistically significant ($p<0.01$, Table 2).

Histological evaluation

Histological analysis with H&E and MT staining demonstrated superior collagen organization in the treatment groups (Figure 3). Tendons from the control groups were characterized by a disorganized, dense collagen pattern. Conversely, tendons from the treatment groups showed a more regular and aligned collagen fiber structure, indicative of more mature healing.

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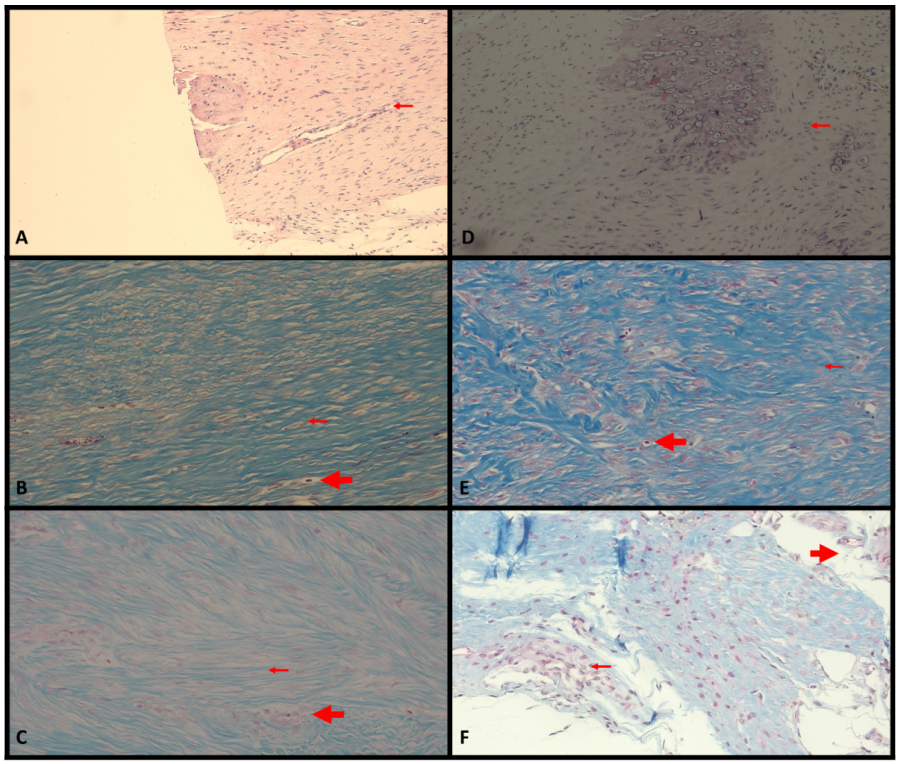

Figure 3. Representative Histological Images of Tendon Healing at 3rd and 6th Weeks in Dermalix and Control Groups. Dermalix Group: (a) 3rd Week Hematoxylin and Eosin Staining, (b) 3rd Week Masson's Trichrome Staining, (c) 6th Week Masson's Trichrome Staining. Control Group: (d) 3rd Week Hematoxylin and Eosin Staining, (e) 3rd Week Masson's Trichrome Staining, (f) 6th Week Masson's Trichrome Staining. Thin red arrows indicate fibroblasts; thick red arrows demonstrate areas of neovascularization.

Table 1. Grouping of samples and procedures to be applied.

		Hist3 n=7 Rat (=14 tendons)		Bmc3 n=7 Rat (=14 tendons)		Hist6 n=7 Rat (=14 tendons)		Bmc6 n=7 Rat (=14 tendons)	
		Hist3-DxG	Hist3-CG	Bmc3-DxG	Bmc3-CG	Hist6-DxG	Hist6-CG	Bmc6-DxG	Bmc6-CG
Number of tendons included in the study		7	7	7	7	7	7	7	7
Initial Procedures	Rupture model created	✓	✓	✓	✓	✓	✓	✓	✓
	Repair	✓	✓	✓	✓	✓	✓	✓	✓
	Dx Application	✓		✓		✓		✓	
Week 3 Procedures	Histological Evaluation (Healing and Adhesion)	✓	✓			✓	✓		
	Biomechanical Evaluation			✓	✓			✓	✓
Week 6 Procedures	Histological Evaluation (Healing and Adhesion)	✓	✓			✓	✓		
	Biomechanical Evaluation			✓	✓			✓	✓

Dx: Dermalix®, Hist3-DxG: Dermalix Histology Group Week 3, Hist3-CG: Control Histology Group Week 3, Bmc3-DxG: Dermalix Biomechanics Group Week 3, Bmc3-CG: Control Biomechanics Group Week 3, Hist6-DxG: Dermalix Histology Group Week 6, Hist6-CG: Control Histology Group Week 6, Bmc6-DxG: Dermalix Biomechanics Group Week 6, Bmc6-CG: Control Biomechanics Group Week 6.

Quantitative analysis showed that the treatment significantly reduced cellular density at the repair site (Table 3). At week 3, the mean number of fibroblasts ($p=0.032$) and fibrocytes ($p<0.001$) was significantly lower in the DxG compared to the CG. This reduction in cellularity persisted at week 6 for both fibroblasts ($p=0.002$) and fibrocytes ($p<0.001$). No significant differences in neovascularization were observed between groups at either time point ($p>0.05$).

Biomechanical testing

Biomechanical testing demonstrated that the treatment significantly improved the tensile strength of the repaired tendons. At week 3, the maximum load to failure was significantly higher in the DxG than in the CG ($p<0.0001$). This enhanced strength was maintained through week 6, with the DxG again showing a significantly greater maximum load compared to the CG ($p=0.029$). Although the elongation

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Table 2. Macroscopic adhesion results of all groups.

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hist3-CG	0	0	1	3	3
Hist3-DxG	1	3	3	0	0
Hist6-CG	0	0	0	3	4
Hist6-DxG	3	3	1	0	0

Hist3-DxG: Dermalix Histology Group Week 3, Hist3-CG: Control Histology Group Week 3, Hist6-DxG: Dermalix Histology Group Week 6, Hist6-CG: Control Histology Group Week 6.

Table 3. Mean number of fibroblasts, fibrocytes and neovascularisation of all groups.

	Hist3-CG	Hist3-DxG	P	Hist6-CG	Hist6-DxG	P
Fibroblast (n, SD)	218.51±65.92	188.37±47.82	**0.032**	141.05±22.32	100.62±35.89	**0.002**
Fibrocyte (n, SD)	32.11±26.58	13.22±13.20	**<0.001**	136.91±31.75	71.88±7.05	**<0.001**
Neovascularisation (n, SD)	5.08±2.01	6.82±4.30	0.655	4.60±2.42	3.45±1.72	0.870

Hist3-DxG: Dermalix Histology Group Week 3, Hist3-CG: Control Histology Group Week 3, Hist6-DxG: Dermalix Histology Group Week 6, Hist6-CG: Control Histology Group Week 6, SD: Standard Deviation.

Table 4. Mean force and distance values of the rupture moment.

	Bmc3-CG	Bmct3-DxG	P	Bmct6-CG	Bmc6-DxG	P
Force (Newton, SD)	9.11±0.91	15.40±3.35	**<0.001**	36.45±13.76	42.94±10.88	**0.029**
Distance (mm, SD)	3.74±0.76	3.86±0.78	0.998	4.05±1.72	5.49±1.67	0.204

Bmc3-DxG: Dermalix Biomechanics Group Week 3, Bmc3-CG: Control Biomechanics Group Week 3, Bmc6-DxG: Dermalix Biomechanics Group Week 6, Bmc6-CG: Control Biomechanics Group Week 6.

at rupture was greater in the treatment groups at both time points, these differences did not reach statistical significance (Table 4).

DISCUSSION

This study investigated the efficacy of a bioabsorbable scaffold loaded with resveratrol (RSV), laminin, and hyaluronic acid (HA), referred to as Dermalix® (Dx), as an adjunctive treatment for primary tendon repair in a rat model. Our findings demonstrate that the local application of this scaffold significantly enhanced the biomechanical strength and histological quality of tendon healing while markedly reducing the formation of peritendinous adhesions.

Initially developed in 2014 by Eroğlu et al. as part of a TUBITAK project, the formulation consists of RSV-loaded hyaluronic acid/Dipalmitoyl phosphatidylcholine microparticles embedded in a 3D collagen-laminin matrix. The patented product (PCT/TR2014/000251) was demonstrated to accelerate wound healing in diabetic rats and was subsequently commercialised in 2018. A prospective clinical study conducted by Çetinkalp et al. confirmed that the local application of Dx reduced oxidative stress in the wound area and was absorbed entirely within 72 hours [8–10].

The positive outcomes align with a growing body of evidence supporting the use of plant-derived bioactive agents in tissue regeneration. Studies show the anti-inflammatory, cardioprotective, neuroprotective, antidiabetic, antitumor, antiviral and anticancer effects of RSV, the main active ingredient in Dx [13,14]. Busch et al. linked the effect of RSV on tenocytes to the upregulation of SIRT-1 genes and the reduction of inflammatory mediators, such as Interleukin-1 Beta. They suggested that it could be used for tendonitis treatments in the future [15]. An animal study reported the positive effects of systemic RSV use on tendon healing [16]. There are also studies showing that it is effective and has no side effects, whether used systemically or locally [17,18]. Recent studies have further supported the therapeutic potential of RSV in tendon healing, especially in metabolically compromised conditions. In a 2021 experimental study, RSV treatment was shown to have protective effects on tendons in an animal model of obesity and insulin resistance by reducing the activity of matrix metalloproteinases (MMP-2 and MMP-9) and maintaining the protein content of tendon tissue. These findings emphasize the role of RSV in preventing catabolism and stability of tendons which is very important in tendon healing [19].

As highlighted in a recent review, RSV's potent antioxidant and anti-inflammatory properties are known to promote cellular function and tissue repair. Our results support the hypothesis that local delivery of RSV via a bioabsorbable matrix can effectively modulate the healing environment [20]. These data align with the findings of the present study, which showed that an RSV-loaded scaffold significantly enhanced tendon healing quality and biomechanical strength, while also reducing adhesion formation. This supports the hypothesis that RSV, when delivered locally through a bioabsorbable matrix, may represent a promising adjunctive strategy in tendon repair.

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Another molecule included in Dx is laminin, a protein associated with the basal lamina that was shown to be positive in murine tendon epitenon by Taylor et al [21]. As a key component of the extracellular matrix, laminin plays a multifaceted role in fibrosis and tendon repair, mediating tissue integrity, cell adhesion, migration, and differentiation. It has been shown that the extracellular matrix is not only structural but also actively directs cellular behaviour during fibrosis development, and proteins such as laminin are decisive in this process [22]. In tendon repair, laminin plays a critical role in achieving biological success criteria such as the orientation of scleraxis-expressing cells, axial collagen alignment, and organization of the tendon-bone junction [23]. It has been reported that laminin-211 provides mechanical stability to the muscle-tendon junction through its association with dystroglycan and integrin α7β1 receptors in cell-matrix interactions, and its deficiency leads to functional loss [24]. Both fibronectin and laminin staining are found in the granulation tissue of healing tendons, indicating that these outer cells are involved in the early healing process [25].

Furthermore, the inclusion of laminin and HA likely contributed to the observed benefits. Laminin, a key extracellular matrix (ECM) protein, is critical for cell adhesion, migration, and the organization of the tendon-bone junction. Similarly, HA is well-established as an anti-adhesion agent that improves tissue gliding without impairing healing. The multifaceted composition of the Dx scaffold appears to create a synergistic effect, enhancing multiple aspects of tendon repair.

Throughout the study, the scaffold was observed to be completely bioabsorbed by the 3-week time point, with no macroscopic remnants or signs of a foreign body reaction. This confirms its suitability as a biodegradable local delivery vehicle that does not require subsequent removal. No signs of systemic side effects or foreign body reactions were observed in any of the treated animals. Despite the lack of pharmacokinetic data, the absence of visible remnants supports the scaffold's complete degradation and localised effect profile.

In a study by Zeytin et al. tendon healing was evaluated histologically and biomechanically on day 14 following systemic RSV administration in diabetic rats. Although the maximum tensile strength was higher in the RSV group, the difference did not reach statistical significance. Histologically, better healing patterns were observed in the RSV-treated group [16]. However, the study relied on semi-quantitative microscopic assessments, and to our knowledge, no previous research has performed quantitative histological evaluation. A key finding of our study was the significant reduction in cellularity (fibroblasts and fibrocytes) in the Dx-treated groups at both 3 and 6 weeks. While early fibroblast proliferation is essential for healing, excessive or prolonged cellular activity can lead to disorganized fibrosis and adhesion formation. Our quantitative analysis, which contrasts with the semi-quantitative methods of previous studies, suggests that the Dx scaffold promotes a more regulated and efficient healing process. The lower cell density, combined with the observed improvement in collagen fiber alignment, indicates a favorable modulation of the inflammatory and proliferative phases of healing, which typically conclude by the third week in rats.

There is evidence demonstrating that Dx accelerates wound healing by mechanically supporting the growth of healing cells, as shown in a previous study. [9]. The biomechanical data further support this interpretation. Tendons treated with Dx demonstrated significantly higher rupture force at both 3 and 6 weeks, suggesting an accelerated transition to the remodeling phase and an earlier restoration of tensile strength. This enhanced mechanical integrity may be due to both the improved collagen organization and the initial structural support provided by the scaffold itself. Interestingly, neovascularization did not differ between the groups, suggesting the primary mechanism of action for Dx involves modulating the cellular and ECM environment rather than directly promoting angiogenesis. Further studies involving specific angiogenic markers could offer more detailed insights into this aspect.

Since Dx also contains hyaluronic acid as part of its bioactive scaffold, our findings are in line with previous studies that reported favourable outcomes with HA-based anti-adhesion agents and high-molecular-weight HA injections [26,27]. These agents were shown to improve range of motion and reduce peritendinous adhesions without impairing tendon healing, which supports the potential of Dx as a multifunctional adjuvant in tendon repair.

Limitations

This study has several limitations. A paired-limb design was used (treatment vs. control in the same animal), which carries a potential risk of systemic crossover effects from the bioactive agents. However, the localized application and significant between-limb differences suggest this effect was minimal. The sample size was relatively small, which may limit the generalizability of our findings. The assessment of collagen alignment was qualitative; future studies would benefit from quantitative image analysis to confirm these observations. Finally, the 6-week follow-up period only covers the early-to-intermediate stages of healing, and long-term studies are needed to assess the final maturation of the tendon and the persistence of the anti-adhesion effect.

This is the first study to use this specific scaffold for subcutaneous tendon repair, and further research is needed to compare its efficacy against other anti-adhesion barriers.

CONCLUSION

This preliminary animal study demonstrated that the local application of an RSV-loaded, bioabsorbable scaffold (Dermalix®) significantly reduced peritendinous adhesion formation and enhanced tendon healing, without compromising biomechanical strength. These results indicate that Dx may be a promising adjunct in primary tendon repairs, especially

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when the risk of adhesion is high. Further research with larger sample sizes, long-term follow-up, and comparisons with other biomaterials is needed to confirm its clinical potential.

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Ethics Committee Approval: All animal procedures were approved by the Bursa Uludağ University Local Ethics Committee for Animal Experiments (Approval number: 2023-03/12) and were conducted under institutional guidelines and national regulations for the care and use of laboratory animals (European Directive 2010/63/EU).

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Conflict of Interest: The authors declare that they have no competing interests.

Author Contributions: Conception: O.G, G.E; Design: O.G, G.E; Supervision: O.G; Materials: O.G, G.E, E.B, E.Y; Data Collection and/or Processing: O.G, G.E, E.B, E.Y; Analysis and/or Interpretation: O.G, G.E, E.B, E.Y; Literature Review: G.E, E.Y; Writing: O.G, G.E, E.B, E.Y; Critical Review: O.G, G.E, E.B, E.Y.

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